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Asymmetric Modular Synthesis of Highly Functionalized Medium-Sized Carbocycles and Lactones via Ring-Closing Metathesis of Sulfoximine-Substituted Trienes

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The asymmetric synthesis of highly substituted medium-sized rings is a topic of considerable interest.^{1–3} Medium-sized carbocycles and lactones for example are found as structural motifs in a number of biologically relevant natural products.^{2–4} In this Communication we describe a new asymmetric synthesis of highly substituted medium-sized carbocycles and lactones. Its key elements are the modular synthesis of sulfoximine-substituted trienes starting from enantiopure allylic sulfoximines and their ring-closing metathesis (RCM).^{2,3}

The successive treatment of the allylic sulfoximine 1^5 with *n*BuLi, 2.1 equiv of ClTi(OiPr)3, 2-butenal, 4-pentenal, and 2-methylpropanal at -78 °C afforded the corresponding sulfoximine-substituted homoallylic alcohols 2a, 2b, and 2c,^{5a} each with \geq 96% de in 70-81% yield (Scheme 1). Their silvlation (ClSiEt₃, DMF, and imidazol) furnished sulfoximines 3a, 3b, and 3c^{5a} in 95-96% yield. The lithiation of the Z-alkenyl sulfoximines^{5b,6} 3a-c with *n*BuLi at -78 °C occurred selectively at the α -position and gave the corresponding Z-alkenyllithium derivatives which suffered at -30 °C a complete isomerization to the E-configured alkenyllithium derivatives^{5b,6} 4a-c. Their treatment with allyl bromide furnished the *E*-configured sulfoximine-substituted trienes 5a-c each as a single isomer in 75-92 overall yield based on 3a-c. The analogous reaction of 4a and 4b with 4-pentanal proceeded efficiently but was nearly unselective in regard to C-5 and gave the E-configured allylic alcohols R-6a, S-6a, R-6b, and S-6b, respectively. Their separation and silvlation (ClSitBuMe2, DMF, and imidazol) afforded the silvl ethers R-7a, S-7a, R-7b, and S-7b, respectively, in high overall yield based on 3a-c. With the enantio- and diastereopure sulfoximine-substituted trienes in hand, their RCM was studied. Treatment of the 1.4.8-triene 5a (0.005 M) with 5 mol % of the ruthenium complex 8^2 in toluene at reflux for 12 h gave the 7-membered carbocycle 9 in 96% yield (Scheme 2). A similar RCM reaction of the 1,4,10-triene 5b with 8 furnished the Z-configured nine-membered carbocycle 10 in 90% yield. Despite their congested structure, the epimeric 1,6,10-trienes R-7a and S-7a also underwent a facile RCM reaction. Thus treatment of R-7a and S-7a (0.005 M) with 5 mol % of 8 in CH₂Cl₂ at reflux for 12 h gave the Z-configured nine-membered carbocycles R-11 and S-11, respectively, in 90% and 80% yield. The configurations of R-11 and S-11 at C-1 were determined by NOE experiments. The treatment of the 1,6,12-triene *R*-7b with 8 under the above conditions afforded the Z-configured 11-membered carbocycle 12 in 70% yield and its *E*-configured isomer 13 in 5% yield.⁷ The configurations of R-12 at C-1 was determined by NOE experiments.

The advantages offered by the modular synthesis of the sulfoximine-substituted trienes are demonstrated by the stereoselective synthesis of triene **14** (Scheme 3) containing a tertiary C-atom. Reaction of the alkenyllithium derivative **4a** with propanal gave a mixture of the epimeric allylic alcohols *R*-**13** and *S*-**14** in 80% yield. Oxidation of the alcohols with Dess–Martin periodinane (DMP)

Scheme 1



afforded enone **15** in 96% yield. The allylation of enone **15** with allylmagnesium bromide gave the tertiary alcohol **16** with 96% de in 90% yield. Thus, contrary to what was observed in the hydroxyalkylation of **4a** and **4b** the sulfoximine group of enone **15** provided a high degree of asymmetric induction in the addition to the carbonyl group. The treatment of the 1,5,9-triene **16** with 5

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mol % of 8 in CH₂Cl₂ at reflux for 16 h furnished the eightmembered carbocycle 17 in 90% yield. The S-configuration of 16 and 17 at C1 was tentatively assigned on the basis of model considerations of the addition of the Grignard reagent to 15.

To demonstrate the synthetic potential of the sulfoximinesubstituted carbocycles, the 11-membered derivative 12 was treated with AcOH/H₂O in THF, which gave the allylic alcohol 18 in 96% yield (Scheme 4). We ascribe the highly selective cleavage of the *t*BuMe₂Si group in the presence of the Et₃Si group to a neighboring effect exerted by the protonated sulfoximine group. Protonation of sulfoximine 12 should give salt 12/AcOH in which the tBuMe₂Si group could be selectively activated toward a nucleophilic attack by an intramolecular hydrogen bond. Oxidation of alcohol 18 with DMP afforded enone 19 in 90%. An example for the facile substitution of the sulfoximine group is provided by the crosscoupling reaction of the alkenyl sulfoximine 9 with LiCuMe₂ (3 equiv) in the presence of ClSiMe₃, which gave the methylated carbocycle 20 in 60% yield (95% based on recovered 9).

Because of the strong interest in the synthesis of medium-sized lactones by RCM,^{1,2,3a} their synthesis starting from the sulfoximinesubstituted diene 3c was probed. The esterification of alcohol 21, obtained by desilylation of 5c (HF/pyridine, THF, 95%), with acrylic acid and pent-4-enoic acid by using DCC/DMAP afforded ester 22 in 47% yield (80% yield based on recovered 21) and ester 23 in 67% yield (97% yield based on recovered 21), respectively (Scheme 5). The treatment of the 1,4,10-triene 22 (0.005 M) with 8 mol % of 8 in toluene at reflux for 16 h gave the Z-configured 9-membered lactone 24 in 87% yield. The similar RCM reaction



of the 1,4,12-triene 23 with 8 furnished the Z-configured 11membered lactone 25 in 81% yield.

In summary, we have developed a highly flexible asymmetric synthesis of functionalized medium-sized carbocycles and lactones through RCM of sulfoximine-substituted trienes. Because of the alkenyl sulfoximine moiety8 of the carbocycles and lactones, further transformations can be envisioned including a Michael addition⁸ followed by a Cl-substitution of the sulfoximine group,^{6b} a Nicatalyzed cross-coupling reaction with organometal reagents9 and a migratory Cl-substitution of the sulfoximine group.¹⁰

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Supporting Information Available: Experimental procedures and characterization data for 2a, 5a, 9, 17, 21, 23, and 25. This material is available free of charge via the Internet at http://pubs.acs.org.

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